Creation of an iliac arteriovenous shunt lowers blood pressure in chronic obstructive pulmonary disease patients with hypertension

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Objective: **Vasodilators are used with caution in patients with chronic obstructive pulmonary disease (COPD). We have developed a device for percutaneous arteriovenous shunt creation in the iliac region to increase cardiac output and oxygen delivery for patients with COPD. Although this device does not cause significant blood pressure changes in normotensive patients with COPD, we hypothesized that arteriovenous shunt creation might cause vasodilator effects in hypertensive patients because of a reduction in vascular resistance.**

Methods: **Twenty-four patients with COPD and hypertension enrolled in an open label study of arteriovenous shunt creation for COPD. We performed cardiac catheterization at baseline and again 3 to 6 months after the procedure. As a safety measure we also recorded office blood pressure at baseline and again after 3, 6, 9, and 12 months.**

Results: **The procedure increased oxygen delivery (1.1-1.4 L.min^{-1}) and cardiac output (6-8.2 L.min^{-1}) ($P < .001$) and lowered both the systemic vascular resistance ($P < .001$) and the pulmonary vascular resistance ($P < .01$). After 12 months, however, the average systolic blood pressure was reduced from 145 to 132 mm Hg ($P < .0001$), and the average diastolic blood pressure was reduced from 86 to 67 mm Hg ($P < .0001$).**

Conclusions: **Percutaneous iliac arteriovenous fistula creation for COPD causes a significant and persistent lowering of blood pressure in patients with co-existing hypertension. (J Vasc Surg 2014;59:1078-83.)**

Vasodilator therapy can worsen patients with chronic obstructive pulmonary disease (COPD).[1-3] The use of nitric oxide, for example, is contraindicated in COPD.[3] Vasodilators (sildenafil, for example) that affect the availability of nitric oxide are also not recommended for patients with COPD.[4] Since many patients with COPD suffer the effects of reduced systemic oxygen transport, we have developed a percutaneous procedure that creates a side to side iliac arteriovenous shunt with the aim of increasing cardiac output and, hence, oxygen delivery for patients with severe COPD.[5] While the procedure has no direct effect on airflow limitation or hypoxemia, some COPD patients have experienced improved exercise capacity[5] and New York Heart Association functional class.[6] To date a significant vasodilator effect has not been described after this procedure.

When upper extremity end to side arteriovenous fistulae are created for dialysis patients, the procedure causes a vasodilator effect through reductions in vascular resistance.[7] Indeed, systolic and diastolic blood pressures are reported to be lower even before dialysis is commenced.[7] Since dialysis shunts have been shown to lower blood pressure through a reduction in vascular resistance, we hypothesized that creation of an arteriovenous shunt for COPD might cause significant vasodilator effects in patients with coexistent hypertension.

METHODS

This report includes all 24 patients with COPD and who had an office-based systolic blood pressure of 130 mm Hg or more at baseline, in spite of antihypertensive therapy, and who underwent percutaneous arteriovenous shunt creation using the Rox Anastomotic Coupler device (Anastomotic Coupler II; Rox Medical, San Clemente, Calif) with subsequent follow-up to 1 year. Full details of these multicenter studies of the effect of

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The sponsor of the study (Rox Medical) participated in the design of the study, analysis of data, and review of the final manuscript. All authors had full access to all study data and the corresponding author had final responsibility for the decision to submit for publication.

Author conflict of interest: Dr Faul is author of patents related to the creation of an arteriovenous shunt for the treatment of chronic obstructive pulmonary disease, heart failure, and hypertension. Dr Faul is a founder of Rox Medical, the sponsor of this study and the manufacturer of the Rox Nitinol Self-expanding Anastomotic Coupler Device. Dr Faul has stock ownership in Rox Medical and has received consultant fees and speaker honoraria from Rox Medical. Sandra Luitjens is an employee of Rox Medical.

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arteriovenous shunt on oxygen delivery in COPD are found at ClinicalTrials.gov, numbers NCT00832611 and NCT00992680. Study protocols were in accordance with the Declaration of Helsinki and were approved by the local Research Ethics Review Committee at each of the participating centers. All patients provided written informed consent prior to all procedures. The study procedures were overseen by a Data Safety and Monitoring Committee, which oversaw the conduct of the study and the safety of the study subjects.

Each patient in this report had systolic blood pressure recordings greater than 130 mm Hg at baseline in spite of antihypertensive therapy and was not known to have a secondary cause of hypertension. All patients were 50 to 80 years old, and had Global Initiative for Obstructive Lung Disease stage II or greater COPD, were without an exacerbation of COPD, and were on stable medication for a minimum of 4 weeks prior to enrollment. The exclusion criteria included a mean pulmonary arterial pressure greater than 35 mm Hg (measured by right heart catheterization), obesity (body mass index greater than 31 $kg.m^{-2}$ male or 32 $kg.m^{-2}$ female), liver cirrhosis, recent stroke or heart failure (within 6 months), unstable coronary artery disease, peripheral vascular disease, and cancer that might adversely affect patient safety. To create an iliac arteriovenous shunt, we deployed an investigational device through a novel delivery system (Fig 1). The device, crossing needle, guidewire, and delivery system are undergoing human clinical trials and have not yet obtained U.S. Food and Drug Administration approval. The shunt is maintained by a single self-expanding nitinol anastomotic coupler (Rox Medical) that was deployed in the iliac region. Vascular access was obtained using standard interventional techniques. After arterial puncture, a coiled guidewire was placed via an introducer into the femoral artery and introduced cephalad into the iliac artery using fluoroscopic guidance (Fig 1, *a*). Next, a straight guidewire was placed into the femoral vein and introduced cephalad into the iliac vein using fluoroscopic guidance. An 11F introducer was placed over the venous guidewire, allowing introduction of a 7F delivery catheter delivery system. Through the 7F delivery catheter system, a 22-gauge crossing needle was tracked up the iliac vein, to a point where the iliac artery and vein cross over one another (Fig 1, *b*). The crossing needle was then pushed through the wall of the iliac vein into the iliac artery (using the coiled guidewire in the lumen of the iliac artery as an anatomical target for the crossing needle). A guidewire was then advanced through the crossing needle from the femoral vein to iliac vein and across the puncture into the iliac artery. The placement of this wire was confirmed by fluoroscopy. The crossing needle was removed from the femoral vein and the coiled guidewire was removed from the iliac artery. Next a self-expanding device was introduced via the 7F delivery system through the femoral vein introducer and along the guidewire that followed a path from femoral vein to iliac vein to iliac artery. The delivery catheter was tracked up through the femoral vein and across the puncture site and into the iliac artery. A self-expanding nitinol anastomotic coupler (Rox Medical) was then deployed so that the expanded arms of the coupler attach to the inner walls of the iliac artery first, followed by a further deployment of the remaining set of expanded arms for their attachment to the inner walls of the iliac vein, and a set of retention arms to maintain the coupler in the proper position (Fig 1, *c*). After removal of the delivery system, a 4-mm balloon catheter was introduced along the guidewire and inserted into the center of the (fluoroscopically visible) anastomotic coupler. The balloon was inflated to further expand the coupler to a 4-mm diameter (Fig 1, *d* and *e*). The balloon was then deflated and removed with the delivery system. To assess whether the procedure was successful, an iliac arteriogram was completed at the end of the procedure to confirm the patency of the shunt. Manual compression was applied to achieve hemostasis at the femoral and arterial puncture sites. Patients were prescribed aspirin and compression stockings after the procedure.

Baseline measurements consisted of vital signs, physical examination, and cardiac catheterization. We did follow-up assessments at 3, 6, 9, and 12 months, which consisted of office blood pressure measurement, physical examination, and surveillance for adverse events. We recorded office blood pressures in accordance with standard Joint National Committee VII guidelines. Patients also underwent repeat cardiac catheterization 3 to 6 months after implantation of the device (creation of an arteriovenous shunt). Although ambulatory blood pressure measurement (ABPM) is considered more robust than office blood pressure measures, the use of ABPM monitors here was considered too onerous for patients with severe COPD who were already undergoing numerous study visits and procedures for this study of oxygen delivery in COPD. Cardiac output was measured in all but five subjects using a thermodilution catheter technique. In five subjects, the baseline and follow-up cardiac output were measured using the Fick technique.

Statistical analysis. We monitored changes in office-based blood pressure over 12 months of follow-up and compared it with baseline blood pressure by repeated measures analysis of variance with pair-wise comparison of significant values. To assess the hemodynamic effect of shunt creation, we compared hemodynamic measures between baseline and repeat cardiac catheterization (between 3 and 6 months after the creation of a shunt) using paired *t*-tests. A P value of less than .05 was regarded as statistically significant. Multiple linear regression analysis was performed to determine whether an association exists between changes in hemodynamic measures and changes in office based blood pressure and age, sex, baseline heart rate, and baseline severity of COPD. Analyses were performed with Microsoft Excel (Microsoft Corp, Redmond, Wash) and Graphpad Prism (GraphPad Prism Corp, San Diego, Calif).

RESULTS

Twenty-four (13 male) COPD patients with a baseline systolic blood pressure greater than 130 mm Hg and a mean postbronchodilator forced expiratory volume in 1

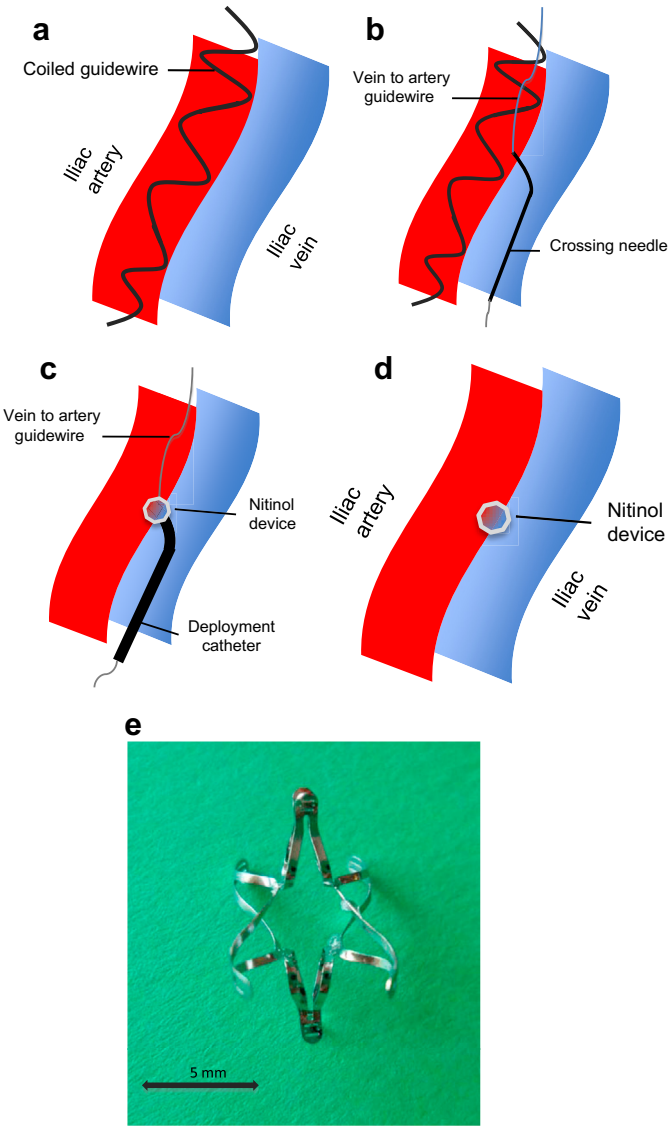

Fig 1. Deployment of the anastomotic clip involves passing a coiled guidewire along the iliac artery to outline the course of the right iliac artery during fluoroscopy **(a)**. Next a 22-gauge curved needle is introduced into the iliac vein and introduced (through the walls of the iliac vein and iliac artery, using the coiled guidewire as a target) into the lumen of the iliac artery. A guidewire is passed through the lumen of this curved needle to confirm access from the iliac vein into the iliac artery during fluoroscopy **(b)**. Using the guidewire that leads from iliac vein to iliac artery as a guide, a 7F delivery catheter is introduced to deploy a nitinol device between the artery and vein, allowing the creation of a 4-mm arteriovenous fistula **(c-e)**. The procedure results in deployment of a self-expanding nitinol device that creates a central lumen of 4-mm diameter allowing a shunt of blood from iliac artery to iliac vein.

second = 30% predicted successfully underwent creation of an arteriovenous shunt using a percutaneously deployed nitinol anastomotic coupler device (Rox Medical) in the iliac region. Their demographic details are contained in Table I. Two-thirds of patients (n = 16) had a systolic blood pressure greater than 140 mm Hg at baseline, while 21% had a systolic blood pressure greater than 160 mm Hg. There was no institution, sex, or race/ethnic based difference in outcome. Patients took, on average, two antihypertensive medications, with 29% receiving an angiotensin-converting enzyme inhibitor, 17% an angiotensin II receptor blocker, 17% beta-blockers, 25% calcium-channel blockers, and 8% direct vasodilators. Almost one-half (46%) of the hypertensive patients also took diuretics (Table I).

Cardiac catheterization revealed increases in cardiac output (from 6 [standard deviation (SD), 2] $L.min^{-1}$ at baseline to 8.4 [SD, 3] $L.min^{-1}$; $P < .001$) and oxygen delivery (from 1091 [SD, 432] $mL.min^{-1}$ to 1441 [SD, 518] $mL.min^{-1}$; $P < .001$), accompanied by reductions

Table I. Baseline demographics of the 24 patients with chronic obstructive pulmonary disease (COPD) and high blood pressure who underwent creation of an arteriovenous shunt

No. of patients	24
Age, years	65 (6)
Male sex	54%
Body mass index, $kg.m^{-2}$	25 (5)
Cigarette consumption, pack years	47 (25)
Systolic blood pressure, mm Hg	145 (12)
Diastolic blood pressure, mm Hg	86 (13)
Mean arterial blood pressure, mm Hg	105 (12)
Serum creatinine, mg/dL	0.84 (.26)
Diuretic	46%
ACE inhibitor	29%
Angiotensin receptor blocker	17%
Beta-blocker	17%
Vasodilator (nitrate)	8%
Calcium channel blocker	25%
Postbronchodilator FVC, % predicted	68 (22)
Postbronchodilator FEV_1, % predicted	30 (11)
PaO_2 mm Hg on room air	63 (9)
$PaCO_2$ mm Hg on room air	42 (6)

ACE, Angiotensin-converting enzyme; *FEV,* forced expiratory volume; *FVC,* forced vital capacity; *$PaCO_2$,* partial pressure of carbon dioxide; *PaO_2,* partial pressure of oxygen; *SD,* standard deviation.
Data are presented as mean (SD).

Table II. Hemodynamic values at baseline and on repeat cardiac catheterization postinsertion of an arteriovenous shunt anastomotic coupler device (Rox Medical, San Clemente, Calif) (n = 23)

	Baseline	*Repeat*	P *value*
Heart rate, bpm	91 (16)	92 (16)	.85
Mean arterial pressure, mm Hg	106 (12)	97 (12)	.001
Right atrial pressure, mm Hg	8 (4)	9.5 (4)	.17
Cardiac output, $L.min^{-1}$	6 (2)	8.4 (3)	<.001
Oxygen delivery, $mL.min^{-1}$	1091 (432)	1441 (518)	<.001
Systemic vascular resistance, dynes	1457 (483)	930 (335)	<.001
Mean pulmonary arterial pressure, mm Hg	25 (5)	29 (6)	<.01
Mixed venous oxygen saturation, %	73 (6)	79 (5)	<.001
Pulmonary capillary wedge pressure, mm Hg	12.2 (5)	15.5 (7)	.01
Pulmonary vascular resistance, dynes	190 (117)	140 (77)	<.01

SD, Standard deviation.
Repeat cardiac catheterization was performed between 3 and 6 months after creation of an arteriovenous shunt.
Data are presented as mean (SD).

in mean arterial pressure (106 [SD, 12] to 97 [SD, 12] mm Hg; $P < .001$), systemic vascular resistance (1457 [SD, 483] to 930 [SD, 335] dynes; $P < .001$), and pulmonary vascular resistance (190 [SD, 117] to 140 [SD, 77] dynes; $P < .01$). Although there was no significant change in right atrial pressure or heart rate, there were small but significant increases in pulmonary arterial pressure (25 [SD, 5] mm Hg at baseline to 29 [SD, 6] mm Hg at follow-up; $P < .01$), and pulmonary capillary wedge pressure (12.2 [SD, 5] mm Hg at baseline to 15.5 [SD, 7] mm Hg at follow-up; $P = .01$; Table II). Multivariable regression revealed an association between changes in cardiac output and changes in pulmonary vascular resistance ($P < .05$) and between changes in cardiac output and changes in systemic vascular resistance ($P < .05$). Changes in pulmonary capillary wedge pressure were associated with changes in systemic vascular resistance ($P < .05$) but were not associated with changes in pulmonary vascular resistance.

The average blood pressure measurements were 145/86, 139/76, 130/71, 132/74, and 132/67 mm Hg at baseline, 3, 6, 9, and 12 months, respectively (Figs 2 and 3). By the end of the study period (12 months), the creation of the shunt had significantly reduced both systolic and diastolic blood pressures; the systolic blood pressure was reduced from 145 (SD, 12) to 132 (SD, 18) mm Hg and the diastolic blood pressure was reduced from 86 (SD, 13) to 67 (SD, 13) mm Hg ($P < .0001$). Multiple comparison testing revealed significant differences in systolic blood pressure between baseline and 6 months, baseline and 9 months, and baseline and 12 months. Multiple comparison testing revealed significant differences in diastolic blood pressure between baseline and 3 months, baseline and 6 months, baseline and 9 months, and baseline and 12 months and a significant difference was also seen between 3 and 12 months. Multivariable analysis showed a significant association between baseline diastolic blood pressure and changes in diastolic pressure at 12 months ($P < .02$) but failed to show a clear association between

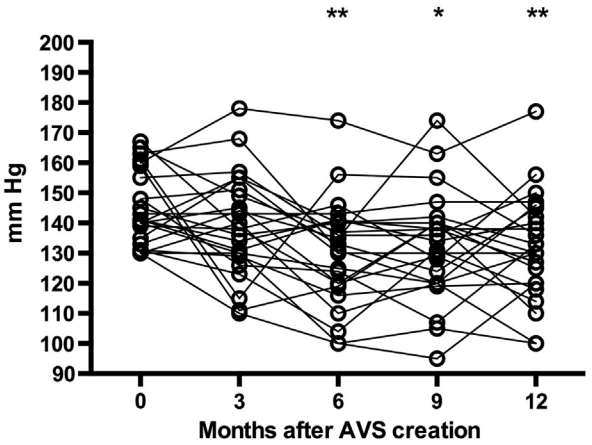

Fig 2. Systolic blood pressure recordings (mm Hg on Y axis) at baseline 0 and 3, 6, 9, and 12 months after creation of an iliac arteriovenous shunt (*AVS*) using an anastomotic coupler device (Rox Medical, San Clemente, Calif) ($P < .0001$, by analysis of variance). Postanalysis testing revealed significant differences between baseline and 6 months (**$P < .01$), baseline and 9 months (*$P < .05$), and baseline and 12 months (**$P < .01$).

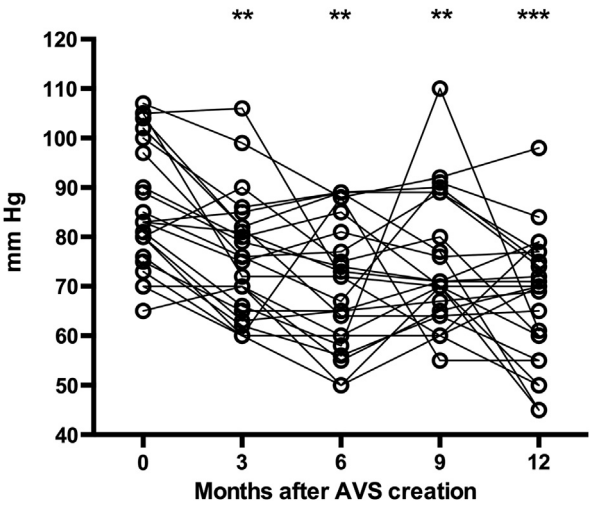

Fig 3. Diastolic blood pressure recordings (mm Hg on Y axis) at baseline 0 and at 3, 6, 9, and 12 months after creation of an iliac arteriovenous shunt (*AVS*) using an anastomotic coupler device (Rox Medical, San Clemente, Calif) ($P < .0001$, by analysis of variance). Postanalysis testing revealed differences between baseline and 3 months ($**P < .01$), baseline and 6 months ($**P < .01$), baseline and 9 months ($**P < .01$), baseline and 12 months ($***P < .001$).

blood pressure reduction and any of the following: age, sex, baseline heart rate, baseline severity of COPD (partial pressure of oxygen in arterial plasma and forced expiratory volume in 1 second). At baseline, patients were taking an average of two antihypertensive medications, which did not change during follow-up.

The median procedure time (from skin to skin) was 53 minutes (range, 20 minutes to 2 hours and 15 minutes). Among the 24 patients who underwent arteriovenous shunt creation, the procedure was completed without complication in 20 patients. Within 7 days of the procedure, two patients developed pseudoaneurysm at the femoral access site, which was successfully treated with manual compression, and did not have any further complication; one patient developed mild chest pressure and chest pain, which resolved; and one patient developed a clot around the shunt which resolved after anti-coagulant therapy. Late adverse events included four patients who developed deep venous thrombosis (resolved with 3 months of anticoagulation) and another patient in whom the shunt was closed (at 11 months) because of a perceived lack of clinical improvement. Four patients developed a venous stenosis of the iliac vein cephalad to the device. Two of these cases were initially treated with dilatation; however, the stenosis recurred and was subsequently treated with stent placement. The remaining two subjects with venous stenosis were all successfully treated with stent placement without recurrence. In one case, the stent was undersized, resulting in dislodgement and migration into the right ventricle. The stent was retrieved and repositioned in the left iliac vein with no sequelae, and the venous stenosis was successfully treated with an appropriately sized self-expanding stent. Our patients with a long-term stent placement for the venous stenosis report good long-term efficacy without any adverse effect. There was no death during the 12-month follow-up period.

DISCUSSION

Percutaneous iliac arteriovenous fistula creation causes a significant and sustained vasodilator effect in hypertensive COPD patients. One year after device implantation the systolic blood pressure is reduced by an average of 13 mm Hg and the average drop in diastolic blood pressure is 19 mm Hg. The reduction in diastolic pressure is significantly associated with higher baseline diastolic blood pressure recordings, suggesting that the vasodilator effect is greater in patients with more severe hypertension. Almost all these hypertensive patients have lower blood pressure after the procedure, and the proportion of patients with a systolic blood pressure greater than 140 mm Hg is reduced from 67% at baseline to 33% after 12 months. Thus, when planning iliac arteriovenous fistula creation in COPD patients with hypertension, one should consider the procedure can have a significant vasodilator effect—an effect that might not be universally well tolerated by patients with severe COPD. In our experience, normotensive subjects do not develop a significant lowering of blood pressure after this new procedure. In one single center study using similar techniques for iliac arteriovenous fistula creation, a shunt significantly increased cardiac output and oxygen delivery, but no comment was made about blood pressure lowering.[6]

Percutaneous creation of an iliofemoral arteriovenous shunt appears to cause a sustained drop in systemic arterial blood pressure in hypertensive COPD patients. Our demonstration of significant hemodynamic changes (measured by cardiac catheterization), combined with progressive reductions in office based blood pressure recordings after percutaneous iliac arteriovenous shunt creation suggest a significant blood pressure lowering. This new technique employs iliofemoral vascular access with a catheter guidance system and (through a series of crossing needles and dilators) creation of a 4-mm shunt between the iliac artery and iliac vein. The shunt remains patent (96% patency rate at 1 year) with the deployment of a self-expanding nitinol vascular anastomotic coupler. In spite of the significant vasodilator effect, the presence of this device is remarkably well tolerated, even in these elderly patients with advanced lung disease. It is somewhat reassuring that heart rates remained unchanged at all time points after shunt creation, and although there was no significant adverse cardiac effect in this cohort of patients, the procedure has the potential to cause adverse events in patients with severe COPD. Arteriovenous shunt creation is a common procedure in renal patients and has a predictable long-term safety record.[8] Cardiac patients who develop moderate femoral arteriovenous shunts after coronary angioplasty have no increase in adverse cardiac events.[9] In addition to a lowering of blood pressure, other

procedure-related complications, such as bruising, are self-limiting, and the commonest late complication with this percutaneous procedure is venous stenosis. Our approach is to treat venous stenosis with a self-expanding stent because angioplasty allows recurrence. Although heart failure occurs after large arteriovenous shunt formation (aortocaval and large arteriovenous shunts),[10,11] the risk of heart failure is not increased in dialysis patients with moderate or small shunts. Indeed, in dialysis patients who have arteriovenous shunts, the cardiovascular risk is less than in patients who receive dialysis through catheters,[12] suggesting that observations about heart failure and pulmonary hypertension in the presence of arteriovenous shunts may relate to (1) the size of the shunt and (2) the severity of underlying disease rather than an effect of the procedure alone.[12-14] Here we chose a moderate shunt with a diameter of 4 mm, because smaller fistulae (1-2 mm) can close spontaneously[9] and larger fistulae (7-8 mm or more) carry a greater risk of heart failure.[10,11]

CONCLUSIONS

We cannot exclude the possibility that the blood pressure effects seen here could have been either due to improved medication compliance during the study, or a placebo effect, or a regression to the mean. Thus, while we cannot yet support the use of this procedure for the treatment of hypertension, the antihypertensive effect observed here probably merits further examination in a controlled study of patients with severe, treatment resistant hypertension. Prospective studies of hypertensive patients using ABPM might confirm or even refute our surprising observations and might provide further information about nocturnal dippers and daytime spikes of blood pressure.[15] If future studies of hypertensive patients (without COPD) confirm a significant vasodilator effect, then this novel technique might be explored as a therapeutic option for patients with drug-resistant hypertension.

AUTHOR CONTRIBUTIONS

Conception and design: JF, DS, SB, BS, AJ, JG, ED
Analysis and interpretation: DS, SB, BS, AJ, JG, ED
Data collection: AJ, SL
Writing the article: JF, DS, SB, BS, AJ, JG, SL, ED
Critical revision of the article: JF, DS, SB, BS, AJ, JG, SL, ED
Final approval of the article: JF, DS, SB, BS, AJ, JG, SL, ED
Statistical analysis: DS, SB, JG, SL, ED
Obtained funding: JF
Overall responsibility: JF

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